

the attached pages.

For reasons set forth below, Applicants respectfully request that the rejections be removed and the claims be allowed to issue.

I. The Drawings are Correctly Labeled

The drawings were objected to because Figure 9 was not correctly labeled. In response, Applicants have attached an amended Figure 9, wherein the phrase "Figure 9" has been added to this figure. The change is marked in red. Applicants respectfully request that the Examiner now remove the objection to the drawings.

II. The Abstract Complies with 37 C.F.R. § 1.72

The Abstract of the Disclosure was objected to for exceeding 150 words. In response, Applicants have amended the abstract as indicated herein to fully comply with the length requirements of 37 C.F.R. § 1.72. Applicants respectfully request that the Examiner now remove the objection to the Abstract of the Disclosure.

III. The Title of the Invention is Descriptive

The title of the invention was characterized as non-descriptive. In response, Applicants have amended the title as indicated herein to fully comply with the length and other requirements of 37 C.F.R. § 1.72. Applicants respectfully request that the Examiner now remove the objection to the title of the invention.

IV. The Brief Descriptions of the Drawings are Correct

The Brief Description of the Drawings was objected to for failing to provide the sequence identifiers in the legend to Figure 1 and for failing to refer to both panels of Figure 3. In response, Applicants have amended the specification as indicated herein to include the sequence identifiers in Figure 1 and to refer to both panels of Figure 3. Applicants respectfully request that the Examiner now remove the objection to the Brief Description of the Drawings.

V. The Application Complies with 37 C.F.R. §§ 1.821-1.825

The Examiner noted that the specification contained sequences that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2), but that the application fails to comply with the requirements of 37 C.F.R. §§1.821-1.825 because the sequences that were set forth lack sequence identifiers, were not listed in the paper Sequence Listing that was filed, were not listed in the computer-readable paper Sequence Listing that was filed, and were not subjected to the attorney statement that was filed.

In response, Applicants have amended the specification to replace the previously filed Sequence Listing with the Sequence Listing included herewith. This Sequence Listing contains those sequences included in Figures 1A, 1B, 1C, 1D and 10, as well as all other unique nucleotide sequences of ten base pairs or more in length and all amino acid sequences of four residues or more in length, as set forth in 37 C.F.R. § 1.821(a)(1). Applicants respectfully request that the Examiner now remove the objection to the sequence disclosures of the instant application.

VI. The Claims Have Patentable Utility

Claims 1-11 are rejected under 35 U.S.C. § 101 as lacking utility. Specifically, the Examiner asserts that the subject matter of Claims 1-11, namely an isolated nucleic acid of SEQ ID NO:1, derivatives or fragments of this nucleic acid having functional homology to the peptide encoded by SEQ ID NO:1, nucleic acids that hybridize to SEQ ID NO:1, vectors comprising these nucleic acids, and cells comprising these vectors, is not supported by the specification, because, according to the Examiner, Applicants have not provided "concrete evidence" for the function of the polypeptide encoded by SEQ ID NO:1.

In response, Applicants respectfully direct the Examiner's attention to various parts of the specification, wherein it is disclosed that Applicants were in fact, at the time that the application was filed, in possession of the a full-length Melanoma Differentiation Associated Gene-5 (MDA-5) cDNA (p. 57, lines 4 through 20, *et alia*) and an isolated MDA-5 protein (p. 55, lines 24-30, *et alia*).

Regarding the Examiner's assertion that the disclosure does not provided "concrete evidence" for the function of the polypeptide encoded by SEQ ID NO:1 (the MDA-5 protein), Applicants direct the Examiner's attention to p. 63, line 25 through p. 64, line 20 of the specification, wherein Applicants disclose that the expression of MDA-5 in tumorigenic HO-1 cells dramatically reduced colony formation when compared to HO-1 cells treated by a control vector. *See also* Figure 9. As further noted on p. 70, lines 18-21 of the specification, this reduction in colony formation is even more dramatic in light of the inefficient nature of transfection and the random incorporation of transfected genes into the cellular genome. Thus, Applicants contend that they have demonstrated at least one specific utility for MDA-5, namely as an inhibitor of tumor growth, and that the invention is in fact in a readily available form.

In light of these arguments, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-11 under 35 U.S.C. § 101.

VII. The Claims Satisfy the Written Description Requirement of 35 U.S.C. § 112, first paragraph

Claims 2-11 are rejected under the written description requirement of the first paragraph of 35 U.S.C. § 112 as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner asserts that Claims 2, 3, and 4 are genus claims drawn to any derivative of SEQ ID NO:1 encoding a polypeptide that is functionally equivalent to MDA-5, a fragment of SEQ ID NO:1 encoding a polypeptide having MDA-5 biological activity, and a nucleic acid that hybridizes to SEQ ID NO:1 or its complement, respectively, but that the disclosure does not teach the relationship between the DNA structures and the MDA-5 protein function that is required to support these claims. Claims 5-11 are rejected under the written description requirement of 35 U.S.C. § 112 apparently because they depend from Claims 2 and 4 above.

Applicants respectfully traverse the rejection of these claims. However, in the interest of furthering the prosecution of this case and to bring greater clarity to the claims, Applicants have amended Claim 2 and cancelled claim 3 without prejudice.

As amended, Claim 2 is drawn toward an isolated nucleic acid comprising a nucleic acid sequence encoding a MDA-5 polypeptide having the sequence of SEQ ID NO:2. The specification provides ample support for an MDA-5 polypeptide of SEQ ID NO:2. *See e.g.* p. 24, line 7 through p. 25, line 3 of the specification. *See also* Figure 1A. Thus, Applicants maintain that the specification

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reasonably conveys to one of ordinary skill in the art that the inventors, at the time the application was filed, had possession of the invention as claimed in amended Claim 2.

As regards claim 4, nucleic acids which hybridize to mda-5 are recited at page 9 lines 18-21 of the specification. The status of hybridization methods as techniques routinely used in the art renders hybridizable nucleic acids a defined class of molecules. Accordingly, Applicants were in possession of the subject matter of claim 4 when the application was filed.

The remaining claims 5-11 depend upon claim 1, 2 and/or 4.

Applicants therefore respectfully request that the rejection of Claims 2-11 under the written description requirement of the first paragraph of 35 U.S.C. § 112 be removed.

VIII. The Claims Satisfy the Enablement Requirement of 35 U.S.C. § 112, first paragraph

Claims 1-11 are rejected under the enablement requirement of the first paragraph of 35 U.S.C. § 112 as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which the invention pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner asserts that Claims 1-4, which are directed to isolated nucleic acids comprising SEQ ID NO:1, any derivative of SEQ ID NO:1 encoding a polypeptide that is functionally equivalent to MDA-5, a fragment of SEQ ID NO:1 encoding a polypeptide having MDA-5 biological activity, or a nucleic acid that hybridizes to SEQ ID NO:1 or its complement, respectively, but that the application fails to provide an "established nexus" between the nucleic acid sequences claimed and any of these speculated functions.

In response, Applicants note that, as discussed above for the rejection of Claims 1-11 under 35 U.S.C. § 101, the specification does in fact provide a definitive function for the polypeptide encoded by SEQ ID NO:1, namely as a tumor growth suppressant. In light of this teaching by the

specification, Applicants maintain that one of ordinary skill in the art would be enabled to use the instantly claimed molecules for their intended function as a tumor growth suppressant. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-11 under the enablement requirement of the first paragraph of 35 U.S.C. § 112.

IX. The Claims Satisfy the Requirements of 35 U.S.C. § 112, second paragraph

Claims 2 and 5-11 are rejected under the second paragraph of 35 U.S.C. § 112 as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Claim 2 is held by the Examiner to be vague indefinite for its recitation of the phrase "functional homology" regarding the polypeptides encoded by derivatives of SEQ ID NO:1. The Examiner concedes that the phrase is adequately defined by the specification, but that the metes and bounds of this phrase cannot be established in the absence of concrete knowledge of the function of the polypeptide encoded by SEQ ID NO:1.

In response, Applicants note that Claim 2, as amended, is now directed toward an isolated nucleic acid comprising a nucleic acid sequence that encodes an MDA-5 polypeptide having the sequence of SEQ ID NO:2. Applicants assert that this amendment renders this claim definite, and respectfully request that the Examiner withdraw the rejection of Claim 2 and dependent Claims 5-11 under the second paragraph of 35 U.S.C. § 112.

CONCLUSION

Based on the foregoing remarks and in light of the amendments, Applicants submit that the present application is in condition for allowance. A Notice of Allowance is therefore respectfully requested.

Applicants believe a fee of \$460.00 is due with this response for a three-month extension of time as required under 37 C.F.R. §1.17(a)(3). Applicants further believe that a fee of \$640.00 is due with the Petition to Revive Unintentionally Abandoned Application enclosed herewith. Accordingly, Applicants enclose a check in the amount of \$1100.00 representing the \$460.00 fee for a three-month extension of time as required for small entities under 37 C.F.R. §1.17(a)(3) and the \$640.00 petition fee as set forth in 37 C.F.R. § 1.17(m) for a small entity in compliance with 37 C.F.R. § 1.27(a). Should any additional fees be required, the Commissioner is hereby authorized to charge Deposit Account Number 02-4377. A duplicate copy of this communication is enclosed.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

Respectfully submitted,



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Enclosures

MARKED UP VERSION OF TECHNICAL AMENDMENTSIN THE TITLE:

Please amend the title of the application as follows:

--MELANOMA DIFFERENTIATION ASSOCIATED GENE-5 AND VECTORS AND CELLS
CONTAINING SAME[AND PROMOTER AND USES THEREOF]—

IN THE SPECIFICATION:

Please amend the paragraph beginning on page 4, line 3, of the specification as follows:

--Figures 1A-1D. Sequence of mda-5 and alignment with CARD and RNA helicases.

Figure 1A. Nucleotide sequence (SEQ ID NO:1) and corresponding amino acid sequence (SEQ ID NO:2) of mda-5. Underlined sequences are AUUUA sequences. Bold face sequence is the poly A signal. Figure 1B. Additional nucleotide sequence of mda-5p (SEQ ID NO:4[]). Poly A signal is bold faced. Figure 1C. Alignment of CARD proteins with 50 amino acids near the N-terminal region of MDA-5 (a.a. 125-174 correspond to 1-50). (SEQ ID NOS:5-11[-]) Figure 1D. Alignment of the RNA helicase conserved motif of mda-5 with eIF-4A (SEQ ID NO:12[]) and p68 RNA helicases-2E (SEQ ID NO:13[]).

Please amend the paragraph beginning on page 4, line 33, of the specification as follows:

--Figures 3A-3B. Northern blot analysis of mda-5 expression induced by IFN-β in normal and tumor cell lines. RNA samples were extracted from the indicated cells treated with 2,000 U/ml of interferon-β for 24 hr. Northern hybridization was performed as in Materials and

Methods.-

Please amend the paragraph beginning on p. 17, line 12, as follows:

--In one embodiment of the invention, the promoter comprises the nucleotide sequence shown in SEQ ID NO:3[____].--

Please amend the paragraph beginning on page 57, line 22, of the specification to read:

--Electronic sequence analysis of the MDA-5 protein using motif and profile scans of proteins presently in the protein database identified two conserved domains, a caspase recruitment domain (CARD) and an RNA helicase domain. The CARD domain which was defined by generalized profile alignment within the RAIDD and ICH-1 amino terminal regions, is present in various apoptotic molecules such as Mch6, ICE, ICH-2, c-IAP1, c-IAP2 and Ced-3. Current evidence suggests that the biological role of CARD is the recruitment of caspase to apoptotic signaling receptor complexes (19). The sequence alignment of N-terminal 50 amino acids (aa 125-174) of MDA-5 with other CARD-proteins reveals significant sequence homology at conserved amino acids of CARD (Figure 1B). MDA-5 displays the highest homology to the CARD region of RAIDD, which is involved in TNF-R1-mediated apoptotic signal transduction (Figure 1C) (19). The C-terminal 100 amino acids (aa 722-823) of MDA-5 also show significant sequence homology to the RNA helicase C-terminal conserved domain, which is involved in RNA binding and unwinding of double-stranded RNA (Figure 1D) (20). In addition, as with other RNA helicases MDA-5 also contains an ATPase A and B motif (331-TGSGKT; SEQ ID NO:14 and 443-DECH; SEQ ID NO:15) (Figure 1D) (20). However, MDA-5 has unique features in its helicase C-terminal motif and ATPase A motif. MDA-5 has ARGRA (SEQ ID NO:16) instead of the well-conserved YIHRIGRXXR (SEQ

ID NO:17) motif, which is critical for RNA binding in other RNA helicases (20). The ATPase A motif of MDA-5 (LPTGSGKT; SEQ ID NO:18) is also different from the consensus sequence motif (A/GXXGXGKT; SEQ ID NO:19) found in other RNA helicases (20). Moreover, MDA-5 is the first putative RNA helicase that retains both an altered RNA binding motif and an ATPase A motif. Screening of the SwissProt database for homologous sequences containing both of these motifs identified three yeast hypothetical ORFs encoding putative helicases (Gen Bank Accession Number Q09884, Q58900 and P34529). The unique features conserved in *MDA-5* and these yeast proteins may signify that MDA-5 is a member of a new family of helicases. RNA helicases are known to be involved in diverse cellular processes including RNA splicing, RNA editing, RNA nuclear cytosolic transport, translation and viral replication by ATP-dependent unwinding of dsRNA (20). However, based on the unique structure of MDA-5, it is not possible at present to ascribe a biological role for this new molecule and n[m]EW family of helicases.—

Please amend the paragraph beginning on page 71, line 24 of the specification as follows:

--Another distinct motif present in the MDA-5 protein is a RNA helicase signature domain, which spans the C-terminal half of this molecule. RNA helicase is a family of enzymes with a helicase motif, which potentially catalyzes NTP-dependent dsRNA unwinding activity. Not only are the core residues among the RNA helicases conserved, but also the spaces between these residues are retained in the different RNA helicases. Three main features characterize RNA helicases from the N- to C-terminal, an ATPase A motif (GXXGXGKT), an ATPase B motif (DEAD; SEQ ID NO:20, DEAH; SEQ ID NO:21 or DEXH; SEQ ID NO:22) and a critical domain for RNA interaction (HRIGRXXR; SEQ ID NO:23)[(Dong-chul, correct?)]. RNA helicases are classified into three subgroups based on their ATPase B motifs. RNA helicases are implicated in the majority of

steps associated with RNA processing and transcription, nuclear and mitochondrial RNA splicing, RNA editing, ribosomal biogenesis, nuclear cytosolic RNA export, degradation of nonsense RNA and RNA translation. Hence, RNA helicases affect many biological phenomena including cell differentiation, proliferation, development and viral life cycle. Although the RNA helicases are classified into three subgroups, the biological relevance of these groups remains to be defined. In addition, the enzymatic activity of many putative RNA helicases has not been confirmed, this could partly be because of the absence of the appropriate substrate and standard protocol due to the diversity of these enzymes.—

Please amend the paragraph beginning on page 72, line 13 of the specification as follows:

--Despite the well-conserved attributes of RNA helicases, MDA-5 contains four unique features that could mediate functional divergence. The CARD domain of MDA-5 in its N-terminal region is not found in any previously identified helicases, although the functional significance of this region is currently under investigation. The ATPase A motif of mda-5 is unique and contains LPTGSGKT as opposed to the sequences found in other RNA helicases (GXXGXGKT) and a mutation of the first glycine residue of murine eIF-4A to valine abolishes ATP binding ability. Since leucine is a non-polar amino acid as is valine, but it has a bulkier side chain than valine, MDA-5 may not bind ATP effectively and, hence, may be an ATPase defective helicase or it may require a different energy source and/or metals for activity. This property of MDA-5 may explain the reduction in colony forming efficiency by a expression of a mutant of mda-5 lacking this region of the MDA-5 protein. The HRIGRXXR motif which is critical for RNA binding in vitro is not well conserved in MDA-5 (ARGRI; SEQ ID NO:24). The functional role of such sequence divergence in the MDA-5 protein remains to be determined. Three yeast hypothetical ORFs share specific features of MDA-5

including ATPase and RNA binding sites, but their biological function has not been ascertained. Complementation assays between these proteins can provide insights on functional and evolutionary relationship among these molecules.--

Please amend the paragraph beginning on page 84, line 1, of the specification as follows:

--Abstract of the Disclosure

The invention provides for an isolated nucleic acid encoding Mda-5 polypeptide as shown in SEQ ID NO:1. The invention provides for isolated nucleic acids encoding an Mda-5 polypeptide as shown in SEQ ID NO:1. The invention also provides for isolated nucleic acids comprising derivatives of the sequence of SEQ ID NO:1 that encode polypeptides functionally equivalent to Mda-5. The invention further provides for fragments of the isolated nucleic acid of SEQ ID NO:1 that encode polypeptides having Mda-5 biological activity. Vectors comprising these isolated nucleic acids and host cells comprising these vectors are also provided by the instant invention. [A polypeptide having the sequence shown in SEQ ID NO:2. The present invention provides for an isolated *Mda-5* promoter capable of directing transcription of a heterologous coding sequence positioned downstream therefrom, wherein the promoter is selected from the group consisting of: (a) a promoter comprising the nucleotide sequence shown in SEQ ID NO:3 ; (b) a promoter comprising a nucleotide sequence functionally equivalent to the nucleotide sequence shown in SEQ ID NO: 3; and (c) a promoter comprising a nucleotide sequence that hybridizes to a sequence complementary to the promoter of (a) or (b) in a Southern hybridization reaction performed under stringent conditions. The invention provides for a host cell comprising the recombinant expression construct as described herein. The invention further provides for a method for treating cancer in a subject suffering therefrom which comprises administering to the subject an effective amount of a

pharmaceutical composition which comprises a recombinant expression construct comprising: (a) a nucleic acid molecule that encodes a selected polypeptide; and (b) an *Mda-5* promoter nucleotide sequence operably linked to the nucleic acid molecule of element (a), wherein the coding sequence will be transcribed and translated when in a host cell to produce the selected polypeptide, and the *Mda-5* promoter is heterologous to the coding sequence and a pharmaceutically acceptable carrier.]—

IN THE DRAWINGS:

Please substitute the corrected version of Figure 9 contained herein, wherein the corrections are marked in red on the attached version of the marked-up copy of this figure, for the original Figure 9.

IN THE CLAIMS:

Please amend Claim 2 as follows:

2. (Amended) An isolated nucleic acid comprising a nucleic acid sequence[derivative of the sequence of SEQ ID NO:1] encoding an MDA-5 polypeptide having the sequence of SEQ ID NO:2[which is functionally equivalent to Mda-5].